Claims 10 and 21 were amended to clarify that the "lipid" contemplated under the claim is specifically a "phospholipid."

New claims 57-93 have been added to reintroduce the subject matter of the composition claims that were cancelled in connection with the previous appeal, and to clarify that in addition to the neutral lipid specified in the base claims, the claims are open to the additional inclusion of charged phospholipid species. Support for this can be found in the specification at, for example, page 28, lines 4-8.

B. Comments on Vacatur and Remand

In a decision dated March 28, 2002, the appeal pending in the present case was vacated and remanded to the Examiner for action "consistent with the views" stated in the opinion. The Applicants believe it is appropriate, and will help expedite the resolution of this case, to provide comments and to take certain actions consistent with the Board's opinion. To this end, the Applicants now provide their comments generally in the order set forth in the section of the Board's decision entitled "Remand," which begins at page 11.

The Combination of Evan and Tari ('978) Patent Clearly Teaches Away

In the second section of the Remand, the Board suggested that the combination of the '911 patent with Tari and Evan is more relevant that the previously cited rejection over Tari and Evan alone. Presumably, the reason for this is based at least in part on Applicants' arguments pointing out why the Tari patent was of limited relevance and that the combination of Tari with Evan actually teaches away:

1. With respect to the use of neutral phospholipids for the delivery of antisense nucleotides, the Tari patent stands merely for the proposition that it is

desirable to combine a neutral phospholipid with a neutrally charged antisense so that they are "compatible." [see col. 5, lines 18-22]. The only logical extrapolation from this is that if one contemplates using a *positively* charged antisense, the Tari '978 patent would teach the use of a *negatively* charged lipid, and so on. In other words, the Tari '978 patent *teaches away from* using a neutral lipid in the context of a charged antisense.

2. The Evan patent publication teaches only *negatively* charged bcl-2 antisense molecules (see page 58 – "phosphorothioate," "phosphoroamidate" and 2-O-methylribonucleotide). Thus, the combination of Evan with the Tari '978 patent teaches away from using neutral phospholipids – this combination would suggest instead that one employ positively charged phospholipids. This is consistent with the one example of a lipid disclosed by Evan (by way of the Loke *et al.* 1988 publication referenced on page 59 of Evan), which is itself of positively charged lipid, phosphatidylserine (see top of page 284 of Loke *et al.*)

The '911 Patent Is Not Relevant and Not Prior Art

The Board suggests that the Examiner consider including the '911 patent in the foregoing rejection. [Board decision at pp. 8, 12] However, the '911 patent is neither relevant nor prior art. The '911 patent, just like the present application, is assigned to the Board of Regents of the University of Texas System. As such, it is not available as prior art under any section of 102, and thus not available under section 103.

Cholesterol/French Patent/Zon

The Board, in the paragraph bridging pages 12-13 of the vacatur, instructs the examiner to obtain copies of the French patent and the Zon publication as referenced on page 15 of Evan.

Presumably, the Board's reasoning is in connection with its request to obtain and make these references of record is its perception that that they references teach the combination of antisense compositions with lipid molecules such as cholesterol, noting the comments at the bottom of page 12 and in the first full paragraph of page 13. It is respectfully noted that the claims are now directed specifically to the combination of, *e.g.*, oligonucleotides with a neutral *phospho*lipid. Of course, cholesterol is not a phospholipid. Thus, although the claims do not specifically exclude cholesterol, it is clear that cholesterol itself would not satisfy the requirement of the claims for the inclusion of a phospholipid.

Nevertheless, Applicants have proceeded to obtain a copy of the references requested by the Board, which are enclosed herein. Applicants' representative has reviewed the Zon reference and it does not appear to be particularly relevant to any issue, but the Examiner is encouraged to review this reference as well. As a courtesy, Applicants are enclosing a copy of the French patent as well, although it has not been translated.

No Prima Facie Case

It is respectfully submitted that the combination of Evan and Tari, for the reasons discussed above, do not in and of themselves provide a *prima facie* case of obviousness. Furthermore, since the '911 patent is not prior art, it is not available to support a *prima facie* case.

The Rule 132 Declaration

At pages 15-16 of the vacatur, the Board suggests that absent a clear and definite explanation of the prima facie case from the Examiner, it is difficult to evaluate what weight should be accorded the current Rule 132 declaration. It is of some note, however, that at the bottom of page 15 the Board questions "why would it have been obvious" to select a neutral lipid

for use in the lipid/bcl-2 antisense composition of Evan. The Board is clearly requesting a reasonable explanation of the basis for the obviousness rejection, yet recognizes in the very next sentence that "Rule 132 declaration provides evidence, limited as it may be, that the neutral lipid tested" were different than the results obtained from cationic and anionic lipids.

In short, the Board seems to be saying that this difference between tests comparing neutral lipids to cationic and anionic lipids shows a difference that "may be a sufficient rebuttal of a prima facie obviousness rejection" if Evan is the base reference. We do note that on the top of page 16, the Board suggests that the if Tari and the '911 patent are instead viewed as the closest prior art instead of Evan, that the comparison proffered in the Rule 132 declaration would be entitled to less weight. However, such a rejection is not available to the Examiner in that the '911 patent is not prior art.

Rule 131 Declaration

The closing section of the Board's vacatur deal with the issue of a Rule 131 declaration, submitted to remove an abstract by Tormo and one by Almazon, relating to presentations to the March 1996 AACR meeting. The Board indicates that the Rule 131 declaration was not in compliance with the rules in that it was signed only by inventors Tari and Lopez, and not by inventor Tormo, and the Board suggests that the rejection should be reinstated until a proper 131 declaration is made of record.

In response, Applicants will state that the whereabouts of Dr. Tormo are currently unknown, although a significant amount of effort has previously been expended in an attempt to locate this inventor. For this reason, Applicants' representative has been unable to obtain Dr. Tormo's execution of documents.

However, the Examiner is respectfully requested to review these two abstracts anew, in light of what has been many years of prosecution and new rejections, *etc.* It is respectfully submitted that neither of these references add anything additional to the mix. For example, while the Tomo *et al.* abstract mentions incorporating a bcl-2 antisense in a liposome, it does not appear to teach the make-up of liposome – i.e., whether it incorporates neutral phospholipids or not. Similarly, while Applicants have been unable to find a copy of the Almozon abstract, from the description of that reference contained in the record it, too, apparently fails to teach or suggest the combination of a neutral phospholipid. This is understandable in that at the time *these* rejections were entered, the claims were broadly drawn to the use of any type of lipid, charged or uncharged (see Office Action of July 8, 1997).

C. Conclusions

Applicants have submitted remarks which are believed to place the present claims in condition for allowance. In view of this, Applicants respectfully request that the present claims be passed for allowance. Should the Examiner have any comments or questions with regard to any statements contained herein, or any suggestions as to claim modification, the Examiner is respectfully requested to contact the Applicants' representative listed below at (512) 536-3055.

Please date-stamp and return the enclosed postcard evidencing receipt of these materials.

Respectfully submitted,

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